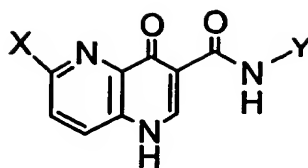


### CLAIMS

1. A pharmaceutical composition comprising a combination of an inverse agonist of the GABA<sub>A</sub>  $\alpha$ 5 receptor subtype; a nicotine receptor partial agonist (NRPA), estrogen, selective estrogen modulators, or vitamin E; and a pharmaceutically acceptable carrier.
2. The pharmaceutical composition of claim 1, wherein the inverse agonist has a functional efficacy at the  $\alpha$ 5 receptor subtype of less than 20%, and a functional efficacy at the  $\alpha$ 1,  $\alpha$ 2 and  $\alpha$ 3 receptor subtypes of between -20 and +20%.
3. A pharmaceutical composition comprising a combination of an inverse agonist of a GABA  $\alpha$ 1 and/or  $\alpha$ 5 receptor subtype; a nicotine receptor partial agonist (NRPA), estrogen, selective estrogen modulators, or vitamin E; and a pharmaceutically acceptable carrier; wherein the GABA<sub>A</sub> inverse agonist has a functional efficacy at the  $\alpha$ 1 and/or  $\alpha$ 5 receptor subtypes of less than -5%, preferably less than -10%, and the efficacy measured at the  $\alpha$ 2 and  $\alpha$ 3 receptor subtypes is greater than 5% or preferably greater than 10%.
4. The pharmaceutical composition of claim 3, wherein the GABA<sub>A</sub> inverse agonist has functional potency (EC50 values) at the  $\alpha$ 1 and/or  $\alpha$ 5 receptor subtypes of 200 nM, preferably less than 150 nM.
5. The pharmaceutical composition of claim 3, wherein the GABA<sub>A</sub> inverse agonist has a functional efficacy at the  $\alpha$ 5 receptor subtype of less than -5%, preferably less than -10%, and the efficacy measured at the  $\alpha$ 1,  $\alpha$ 2 and  $\alpha$ 3 receptor subtypes is greater than 5% or preferably greater than 10%.
6. The pharmaceutical composition of claim 5 wherein the GABA<sub>A</sub> inverse agonist has a functional potency (EC50 values) at the  $\alpha$ 5 receptor subtype of 200 nM, preferably less than 150 nM.
7. The pharmaceutical composition of claim 3 wherein the GABA<sub>A</sub> inverse agonist at the  $\alpha$ 1 and/or  $\alpha$ 5 receptor subtypes has a binding K<sub>i</sub> of 100 nM, preferably less than 30 nM.
8. The pharmaceutical composition of claim 1, wherein the GABA<sub>A</sub> inverse agonist is selected from a compound of Formula I :



I

wherein:

X is hydrogen, halogen,  $-OR_1$ ,  $NR_2R_3$ ,  $C_1-C_6$  alkyl optionally substituted with up to three groups selected independently from halogen and hydroxy, or  $-NR_2R_3$ ; or

5 X is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl, pyridinyl, pyrimidyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzothienyl, each of which is optionally substituted with up to three groups selected from halogen,  $C_1-C_6$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_6$  alkylthio, hydroxy, amino, mono or di( $C_1-C_6$ ) alkylamino, cyano, nitro, trifluoromethyl; or

10 X represents a carbocyclic group ("the X carbocyclic group") containing from 3 - 7 members, up to two of which are optionally hetero atoms selected from oxygen and nitrogen, where the X carbocyclic group is optionally substituted with one or more groups selected from halogen, ( $C_1-C_6$ )alkoxy, mono- or di( $C_1-C_6$ )alkylamino, sulfonamide, aza( $C_3-C_7$ )cycloalkyl, ( $C_3-C_7$ )cycloalkylthio, ( $C_1-C_6$ )alkylthio, phenylthio, 15 or a heterocyclic group; and

Y is lower alkyl having 1 - 8 carbon atoms optionally substituted with up to two groups selected from halogen, ( $C_1-C_6$ )alkoxy, mono- or di( $C_1-C_6$ )alkylamino, sulfonamide, aza( $C_3-C_7$ )cycloalkyl, ( $C_3-C_7$ )cycloalkylthio, ( $C_1-C_6$ )alkylthio, phenylthio, a heterocyclic group,  $-OR_4$ ,  $-NR_5R_6$ ,  $SR_7$ , or aryl; or

20 Y is a carbocyclic group ("the Y carbocyclic group") having from 3 - 7 members atoms, where up to three of which are optionally hetero atoms selected from oxygen and nitrogen and where any member of the Y carbocyclic group is optionally substituted with halogen,  $-OR_4$ ,  $-NR_5R_6$ ,  $SR_7$ , aryl or a heterocyclic group; and

25  $R_1$  is hydrogen, lower alkyl having 1 - 6 carbon atoms, or cycloalkyl having 3 - 7 carbon atoms, where each alkyl may be optionally substituted with  $-OR_4$  or  $-NR_5R_6$ ;

$R_2$  and  $R_3$  are the same or different and represent hydrogen, lower alkyl optionally mono- or disubstituted with alkyl, aryl, halogen, or mono- or di-lower alkyl;

aryl or aryl (C<sub>1</sub>-C<sub>6</sub>)alkyl where each aryl is optionally substituted with up to three groups selected from halogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or mono- or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino;

5 cycloalkyl having 3 – 7 carbon atoms optionally mono or disubstituted with halogen, alkoxy, or mono- or di- lower alkyl; or

-SO<sub>2</sub>R<sub>8</sub>;

R<sub>4</sub> is as defined for R<sub>1</sub>;

R<sub>5</sub> and R<sub>6</sub> carry the same definitions as R<sub>2</sub> and R<sub>3</sub>, respectively;

10 R<sub>7</sub> is hydrogen, lower alkyl having 1 – 6 carbon atoms, or cycloalkyl having 3 – 7 atoms; and

R<sub>8</sub> is lower alkyl having 1 – 6 carbon atoms, cycloalkyl having 3 – 7 carbon atoms, or optionally substituted phenyl;

or an isomer or hydrate thereof, or a pharmaceutically acceptable salt thereof.

9. The pharmaceutical composition of claim 1, wherein the GABA<sub>A</sub>  
15 inverse agonist is selected from the group consisting of:

N-n-Butyl-6-chloro-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-n-Butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Ethylthio)ethyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-  
carboxamide;

20 N-n-Pentyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Tetrahydrofuranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-  
naphthyridine-3-carboxamide;

25 N-Isoamyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-  
carboxamide;

N-(3-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-  
carboxamide;

N-(3-Ethoxy)propyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-  
carboxamide;

30 N-2-(2-Methyl)butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-  
carboxamide;

N-5-Pentanol-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-  
carboxamide;

N-Benzyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

5 N-(4-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4/5-Imidazolyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

10 N-(3-Thienyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Tetrahydropyranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

15 N-(3,5-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

20 N-(4-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Methylbenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Thienyl)methyl-6-(2-methoxyethoxy)-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

25 N-(2-Thienyl)methyl-6-morpholino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Thienyl)methyl-6-dimethylamino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

30 N-(4-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide hydrochloride; and

N-[4-(Imidazolylmethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide.

10. The pharmaceutical composition of claim 1 in which the NRPA is selected from the group consisting of:

- 5 9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-flouro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
10 9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
15 9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
20 9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-propyl)- 1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
25 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
30 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

- 9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-on ;
- 9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;
- 5 9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;
- 9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
pyrido[1,2a][1,5]diazocin-8-one;
- 10 6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-  
triene;
- 5-oxo-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;
- 6-oxo-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;
- 4,5-difluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 5-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene-4-carbonitrile;
- 15 4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 5-ethynyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene-4-carbonitrile;
- 6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-  
2(10),3,8-triene;
- 10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 20 4-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 4-methyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 4-trifluoromethyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 4-nitro-10-azatrichylo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 7-methyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,5,8-  
tetraene;
- 25 6-methyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,5,8-  
tetraene;
- 6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,5,8-  
tetraene;
- 30 6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-  
2(10),3,5,8-tetraene;
- 6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-  
pentaene;
- 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-pentaene;

- 14-methyl-5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-pentaene;
- 5-oxa-7,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,6,8-tetraene ;
- 6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,6,8-tetraene;
- 4-chloro-10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-4-yl cyanide;
- 1-(10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
- 10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-4-ol;
- 7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2,4(8),6,9-tetraene;
- 4,5-dichloro-10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-5-carbonitrile;
- 1-[11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
- 1-[11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-5-yl]-1-propanone;
- 4-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-5-carbonitrile;
- 5-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-4-carbonitrile;
- 6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 6-methyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 5,6-dimethyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;
- 5-methyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;
- 6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 5,8,15-triazatetracyclo[11.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]heptadeca-2(11),3,5,7,9-pentaene;
- 7-methyl-5,8,15-triazatetracyclo[11.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]heptadeca-2(11),3,5,7,9-pentaene;

- 6-methyl-5,8,15-triazatetracyclo[11.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]heptadeca-2(11),3,5,7,9-pentaen ;
- 6,7-dimethyl-5,8,15-triazatetracyclo[11.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]heptadeca-2(11),3,5,7,9-pentaene;
- 5        7-oxa-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 10       6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;
- 7-methyl-5-oxa-6,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;
- 4,5-difluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 15       4-chloro-5-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 5-chloro-4-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 4-(1-ethynyl)-5-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 5-(1-ethynyl)-4-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 5,6-difluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2,4,6-triene;
- 20       6-trifluoromethyl-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2,4,6-triene;
- 6-methoxy-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-6-ol;
- 6-fluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-5-ol;
- 25       4-nitro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 5-nitro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;
- 5-fluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene; and
- 6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene and their pharmaceutically acceptable salts and their optical isomers.
- 30       11. The pharmaceutical composition of claim 1, in which the NRPA is selected from the group consisting of:
- 9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-flouro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;



- 9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-
- 5 pyrido[1,2a][1,5]diazocin-8-one;  
 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-  
 pyrido[1,2a][1,5]diazocin-8-one;  
 9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
 pyrido[1,2a][1,5]diazocin-8-one;
- 10 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-  
 pyrido[1,2a][1,5]diazocin-8-one;  
 6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-  
 2(10),3,8-triene;
- 15 4-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;  
 4-trifluoromethyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;  
 4-nitro-10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;  
 6-methyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,5,8-  
 tetraene;
- 20 6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-  
 pentaene;  
 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-pentaene;  
 5-oxa-7,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,6,8-tetraene;  
 6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,6,8-
- 25 tetraene;  
 10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-4-yl cyanide;  
 1-(10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;  
 11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-5-carbonitrile;  
 1-[11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
- 30 1-[11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-5-yl]-1-propanone;  
 4-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-5-carbonitrile;  
 5-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-4-carbonitrile;  
 6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-  
 tetraene;

6-methyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;

5        6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;

5,6-difluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2,4,6-triene;

10       6-trifluoromethyl-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2,4,6-triene;

6-methoxy-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene;

6-fluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene; and

11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-5-ol and

their pharmaceutically acceptable salts and their optical isomers.

15       12.    The pharmaceutical composition of claim 1, wherein the GABA<sub>A</sub> inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

20       13.    A method for treating a cognitive disorder in a mammal, comprising administering to a mammal in need of said treatment an effective amount of a combination comprising a GABA<sub>A</sub> α5 receptor subtype; and a nicotine receptor partial agonist (NRPA), estrogen, selective estrogen modulators, or vitamin E.

14.    The method of claim 13, wherein the a GABA<sub>A</sub> α5 receptor subtype and the NRPA are administered simultaneously.

25       15.    The method of claim 13, wherein the a GABA<sub>A</sub> α5 receptor subtype and the NRPA are administered sequentially.

30       16.    The method of claim 13, wherein the GABA<sub>A</sub> inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.